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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,452	09/24/2003	Boris Tabakoff	UTC-07983	8035

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EXAMINER
POHNERT, STEVEN C

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,452	TABAKOFF ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *13-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, (claims 1-12 &26-32) in the reply filed on 7/24/2006 is acknowledged.

Drawings

2. The drawings are objected to because Figure 2 depicts the adenylyl cyclase 7 gene, which the specification and legend teach is 73 kb, however the region bracketed under the gene appears to suggests the coding sequencing is 73 kb. It is recommended that the figure 73 should be amended to eliminate the 73kb brackets to eliminate ambiguity. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner,

the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-12, 26-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1-12, 26-32 encompasses a method of identifying individuals predisposed to "major depressive disorder" by detecting "any" polymorphism in "any" adenylyl cyclase 7 (AC7) allele in "any" male or female subject of "any" race. Claim 2 is drawn to a "repeat polymorphism", while claim 3 limits the polymorphism to $[AACA]_7$. Claims 4, 5, and 6 limit the subject to Caucasians, females, and subjects that are alcohol dependent, respectively. The claims set forth the structural requirement "any" polymorphism of AC7 are indicative of predisposition to major depressive disorders, although lacking guidance on a functional relationship of how any AC7 polymorphism is associated with major depressive disorders.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches

adenylyl cyclase 7 (AC7) is a 6196 nucleotide cDNA comprising 73,020 nucleotides on chromosome 16 from bp 37,275,848 to 37,348, 868. The specification teaches, "'gene' encompasses both cDNA and genomic forms of a gene" (se page 7, lines 9 and 10). The specification further teaches the $[AACA]_7$ polymorphism of AC7 occurs in the 3'UTR and does list in table 2 repeat polymorphisms $[AACA]_5$ and $[AACA]_6$. The specification does not teach the location of the $[AACA]_7$ polymorphism in the 3'UTR. The specification does not teach any AC7 polymorphism, except $[AACA]_5$, $[AACA]_6$, and $[AACA]_7$. Although the specification lists $[AACA]_5$ and $[AACA]_6$ in table 2, it does not teach any phenotype associated with these polymorphisms. Further, the specification does not teach how the $[AACA]_7$ genotype or any other AC7 polymorphism alters AC7 function resulting in major depressive disorders. The specification further teaches a subject is "any" human healthy or predisposed to major depressive disorders.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches the sequence of AC7, as SEQ ID NO. 1. The specification further teaches a repeat polymorphism is a dinucleotide, trinucleotide, tetranucleotide or pentanucleotide repeat (see page 8, lines 28-29).The specification further teaches the $[AACA]_7$ repeat polymorphism of AC7 (AC7.R7) occurs in the 3'UTR, and lists in table 2 repeat polymorphisms $[AACA]_5$ and $[AACA]_6$. The specification does not teach the location of the $[AACA]_7$ polymorphism in the 3'UTR or if the location of $[AACA]_7$ polymorphism in the polymorphism is important in diagnosis. The specification does not teach any other AC7 polymorphism, except $[AACA]_5$, $[AACA]_6$, and $[AACA]_7$.

The specification further does not teach how the $[AACA]_7$ polymorphism alters the structure, function, or expression of AC7. The specification teaches studies only in Caucasian populations and teaches a positive association with Caucasian. Caucasian populations are not representative of "any" human, as Caucasian females are also not representative of "any" females.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. The instant case the specification provides the $[AACA]_7$ polymorphism of the 3'UTR. The specification does not teach how the$[AACA]_7$ polymorphism or any other polymorphism of AC7 alters the structure, function or expression of AC7. The specification does not teach how altered function of AC7 or AC7 polymorphisms result in predisposition to major depressive disorders. The specification does not teach how to identify any other AC7 polymorphisms. The claims read in light of the specification encompass any polymorphism of the 73 kb AC7 nucleic acid molecule. The claims read in the light of the specification would further encompass any number of dinucleotide, trinucleotide, tetranucleotide or pentanucleotide repeats as well as any SNP, insertion, or deletion anywhere in the AC7 gene, thus encompassing thousands of potential polymorphism. Each polymorphism would result in a distinctly different AC7 gene, as it would have a altered chemical composition and structure. Further repeat polymorphisms claimed are not limited to the UTRs, but also the coding sequence, thus further altering structure,

and function of AC7. This would encompass an enormous number of nucleic acid samples, as there 73,000 nucleotides in the AC7 genomic sequence.

In the instant application, the provided information regarding nucleic acid adenylyl cyclase 7 polymorphisms, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed. Further the specification does not teach how AC7 polymorphisms result in a predisposition to major depressive disorders. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding adenylyl cyclase 7 polymorphisms is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules encompassed by the genus of "any" polymorphism or "any" repeat polymorphism in the adenylyl cyclase 7 gene.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

5. Claims 1-12, 26-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying Caucasian females and Caucasian alcohol dependent females predisposed to "major depressive disorders" by detecting the presence of the $[AACA]_7$ polymorphism in the 3' UTR, does not reasonably provide enablement for identifying any human, or any female predisposed to "major depressive

disorders" by detecting the presence the of "any" polymorphism in adenylyl cyclase 7 (AC7). The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention there are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims encompass identifying human subjects predisposed to major depressive disorders by detecting the presence of "any" AC7 polymorphism in "any" male or female subject of "any" race or "any" Caucasian. The claims are further drawn to "any" repeat polymorphisms "any where" in the 73 kb AC7 genomic sequence.

The amount of direction or guidance and the Presence and absence of working examples in the specification.

The instant specification teaches the sequence of AC7, as SEQ ID NO. 1. The specification further teaches a repeat polymorphism is a dinucleotide, trinucleotide, tetranucleotide or pentanucleotide repeat (see page 8, lines 28-29).The specification further teaches the $[AACA]_7$ repeat polymorphism of AC7 (AC7.R7) occurs in the 3'UTR, and lists in table 2 repeat polymorphisms $[AACA]_5$ and $[AACA]_6$. The specification does not teach the location of the $[AACA]_7$ polymorphism in the 3'UTR or if the location of $[AACA]_7$ polymorphism in the polymorphism is important in diagnosis. The specification does not teach any AC7 polymorphism, except $[AACA]_5$, $[AACA]_6$, and $[AACA]_7$. The specification does not teach any other AC7 repeat polymorphism. The specification further does not teach how the $[AACA]_7$ polymorphism alters the structure, function, or expression of AC7. The specification does not teach how "any" AC7 polymorphism or AC7.R7 polymorphism functionally results in predisposition to major depressive disorders, such that a skilled artisan could form a predictive relationship between "any" AC7 polymorphism and major depressive disorders.

The specification teaches $[AACA]_5$ and $[AACA]_6$ polymorphisms in table 2, as a variable examined. The specification is silent on a statistical relationship of $[AACA]_5$ and $[AACA]_6$ polymorphisms with major depressive disorders. The specification's silence on the role of $[AACA]_5$ and $[AACA]_6$ suggests these repeat polymorphisms are not indicative of depression in any human. This silence further suggests the only repeat polymorphism predictable of depression is $[AACA]_7$,making $[AACA]_5$ and $[AACA]_6$ unpredictable markers of major depressive disorders.

The specification further teaches a study of 746 Caucasian individuals (see page 20, line 18, and table1). The specification further asserts a statistically significant association between AC7.R7 allele and platelet forskolin stimulated adenylyl cyclase activity (see page 20 lines, 23-25 and table 3). The specification further asserts that the association between AC7.R7 and platelet forskolin stimulated adenylyl cyclase activity is not present in males (see page 23, lines 6-8, table 3 and 4), but not females (see table 5). The association between the platelet adenylyl cyclase activity, AC7.R7, and major depressive disorders is unclear.

The specification further teaches in table 6 there is a no statistically significant association between the AC7.R7 genotype and familial depression in 540 males ($p=0.27$), but there is a statistically significant association familial depression and familial depression in 206 females ($p=0.008$), 122 alcohol dependent females ($p=0.01$). This statistically significant association familial depression with AC7.R7 in females appears significant enough to make the association between AC7.R7 and familial depression statistically significant upon combination of the male and female groups, although the relationship is not significant in the male group alone. The specification further teaches the odds ratio was 0.7 indicating a potential protective effect of having the AC7.R7 allele as part of a male's genotype(see page 28, lines 14-15). This suggests that not only is the AC7.R7 not a marker of depression in males, but also protects males from depression. The specification further teaches that when comparing females with familial depression to those with no family history results in a more statistically significant association with AC7.R7 in 133 females ($p=0.005$) and alcohol

dependent females (p=0.002). Further there is statistically significant in relationship between AC7.R7 and familial depression compared to non-familial depression79 females (p=0.01), but not 60 alcohol dependent females (p=0.06).

The specification does not teach that broadly any AC7 polymorphism is an identifying marker of depression in any non-Caucasian females, males of any race, or alcohol dependent males. The specification further teaches the odds ratio was 0.7 indicating a potential protective effect of having the AC7.R7 allele as part of a male's genotype(see page 28, lines 14-15). This suggests that not only is the AC7.R7 not a marker of depression in males, but also protects males from depression.

The specification does not teach how any polymorphism in AC7 alters AC7 expression, structure or function. The specification does not teach any polymorphism or repeat polymorphism in AC7 other then the AC7.R7 polymorphism, although listing $[AACA]_5$ and $[AACA]_6$. The specification does not teach any guidance as to why an $[AACA]_7$ but, not an $[AACA]_5$ and $[AACA]_6$ polymorphism results are correlative of depression for the skilled artisan to predictably determine what other alleles would be associated with major depressive disorders. The specification further does not teach a predictive relationship between any AC7 polymorphisms and major depressive disorders, except when $[AACA]_7$. The specification does not teach how "any" AC7 polymorphism or AC7.R7 polymorphism functionally results in predisposition to major depressive disorders, such that a skilled artisan could form a predictive relationship between "any" AC7 polymorphism and major depressive disorders.

The teachings of the specification suggest the AC7.R7 allele is an unpredictable marker for major depressive disorders in "any" human, as there is no association found in the study of males taught in the specification, but actually a potential protective effect of AC7.R7.

The state of prior art and the predictability or unpredictability of the art:

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated (see abstract). Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, 2001, Vol. 29, pages 306-309,) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, page 20) teaches that it is strikingly common for follow-

up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Further Stephens et al (Science, 2001, volume 293, pages 489-493) teaches SNPs are expressed variably across populations(See abstract). Accordingly, the teachings of the specification regarding a Caucasian population would not provide the skilled artisan with a predictable correlation that the allele, AC7.R7, let alone "any" AC7 allele, would be associated with a major depressive disorder in any population.

As the art teaches association of a polymorphisms are expressed variably across populations, the skilled artisan would be unable to predictably associate "any" AC7 mutation with major depressive disorders in "any" human population. Although there is a statistical association between AC7.R7 and major depressive disorders in Caucasian women, this can not be broadly interpreted to all women because the art teaches polymorphisms are expressed differently across ethnic populations.

The level of skill in the art:

The level of skill in the art is deemed to be high

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between "any" AC7 polymorphism and a

major depressive disorder in "any" human" subject. The specification does teach the AC7.R7 polymorphism is statistically associated with predisposition to major depressive disorders in Caucasian females, and alcohol dependent Caucasian females. However, the specification does not teach AC7.R7 is statistically associated with predisposition to major depressive disorders in any male or any non-Caucasian female. Further the specification teaches the AC7.R7 appears to be associated with a decreased susceptibility to depression in males, which contradicts the claimed invention. The specification does not teach how "any" AC7 polymorphism or AC7.R7 polymorphism functionally results in predisposition to major depressive disorders, such that a skilled artisan could form a predictive relationship between "any" AC7 polymorphism and major depressive disorders.

Experimentation would be replete with unpredictable trial and error analysis because the specification teaches the AC7.R7 polymorphism is both associated with major depressive disorders in Caucasian females and alcohol dependent females, but protective in Caucasian males. The specification does not address the reason for these contradictory findings. The specification further does not teach an association of any other AC7 polymorphism with depression. One of skill in the art would thus have to determine if "any" AC7 polymorphism is statistically associated with depression in "any" human population and further with respect to gender. Further the skilled artisan would have to specifically determine if the AC7.R7 polymorphism is statistically associated with the occurrence of major depressive disorders as in Caucasian women or protective as suggested in Caucasian males. This would require recruitment of an enormous

racially diverse population and undue trial error experimentation to determine if a statistical association of "any" AC7 polymorphism or the AC7.R7 is present and statistically associated with major depressive disorders.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large racially and gender diverse group of subjects to determine if AC7.R7 or any other AC7 polymorphism is associated with the predisposition to major depressive disorders. Further the skilled artisan would have to further consider the specification teaches AC7.R7 is associated with protection from major depressive disorders as in Caucasian males. Further one of skill in the art would have to consider "any" mutation in AC7 and its association with major depressive disorders

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated art, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1-12, 26-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, 3, 26, and 29 are drawn to the "adenylyl cyclase type 7 allele." It is unclear if this is specific mutation of adenylyl cyclase, a specific adenylyl cyclase allele, or any allele of type 7 adenylyl cyclase.

Claim 2 is drawn to a repeat polymorphism. It is unclear if a repeat polymorphism is an insert ional mutation resulting in a nucleotide being repeated (for example ATC repeat polymorphism ATTC), or the duplication of a repetitive sequence.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEHANNE SITTON
PRIMARY EXAMINER
10/6/06